levels were almost comparable in both SA and ACS patients, the levels of B-type natriuretic peptide (BNP) and of C-reactive protein (CRP) were more than two-fold higher in patients with ACS than in SA. Both BNP and CRP are known to be associated with adverse outcome in ACS patients\(^4\), \(^5\) with BNP also having a prognostic role in patients with SA.\(^4\) The BNP levels in the present study were only 38 pg/mL (11.94–99.81) in patients with SA, a range comparable with 36.1 pg/mL (11.3–94.6), a value found in patients with SA who did not have cardiovascular events in a previous study\(^6\) and overlapping with the values of the first and partially the second lower quartiles of BNP, which were not associated with increased risk of cardiovascular events.\(^5\) Secondly, despite continuous levels of adiponectin predicting cardiovascular events in the overall population after adjusting for the presence of ACS (model 2 regression), adiponectin was not significantly associated with the outcome (models 1–4) in patients with ACS, while only in patients with SA predicted the outcome.

Thirdly, the authors did not report the cardiovascular event rate according to SA and ACS, but it is likely that the patients with SA in this study (who had low BNP values) had a better prognosis compared with patients with ACS.

Taken together, these finding raise the strong possibility that an association between adiponectin and prognosis in patients with ACS might not exist, and that the main result of this study may have been driven by the patients with SA. As patients with ACS represent a large part of patients with CAD in clinical practice, the conclusion, therefore, that adiponectin predicts outcome in patients with CAD may be not accurate.

Moreover, the independent predictive value of adiponectin in SA patients might be a spurious finding, as patients with SA and high levels of BNP (>100 pg/mL) were not included in this study. Furthermore, even in the present cohort of SA patients, a hazard ratio = 1.035 may not represent a clinically significant increase in adverse events if the baseline absolute risk of events is low anyway.

Finally, continuous levels of adiponectin did not independently predict the outcome in the overall population and the independent predictive value of a one-quartile adiponectin level increase has not been verified after entering BNP, CRP, and creatinine as covariates in the Cox proportional hazard regression model.

**References**


**Giuseppe Ferrante**

Institute of Cardiology
Catholic University of the Sacred Heart
Largo Agostino Gemelli, 8
00168. Rome
Italy
Tel: +39 06 30154187
Fax: +39 06 3055535
Email: giu.ferrante@hotmail.it

Cardiovascular Department
Royal Brompton Hospital
London
UK

**Nicola Cosentino**

Institute of Cardiology
Catholic University of the Sacred Heart
Largo Agostino Gemelli, 8
00168. Rome
Italy

**Peter Barlis**

Cardiovascular Department
Royal Brompton Hospital
London
UK

**Giampaolo Niccoli**

Institute of Cardiology
Catholic University of the Sacred Heart
Largo Agostino Gemelli, 8
00168. Rome
Italy

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**Association of adiponectin with adverse outcome in coronary artery disease patients: results from the AtheroGene study: reply**

We thank Dr Ferrante et al.\(^1\) for their interest in our work. By enrolling consecutive cath lab patients in the AtheroGene cohort, we had the opportunity to evaluate adiponectin concentrations across the entire range of coronary artery disease (CAD) patients. This may be seen as an advantage, but also implies heterogeneity of the cohort which we addressed by presenting our data in the more homogenous subgroups of patients with stable angina (SAP) and acute coronary syndrome (ACS).

In ACS, we observe a similar magnitude and direction of association. Especially in the categorical analysis, it becomes obvious that high concentrations of adiponectin may be related to higher cardiovascular event rates that can be viewed as confirmatory.\(^2\) For survival analysis, we do provide the number of events, which shows, as expected, a higher event rate for ACS patients. These hypothesis generating results need to be prospectively confirmed in ACS cohorts.\(^3\)

We did not exclude participants on the basis of B-type natriuretic peptide (BNP) concentrations. In Model 2 of the statistical regression analysis, adjusting for ACS, adiponectin concentrations remain related to outcome at the 0.05 level. Only after additional adjustment for BNP in the last model, the association becomes borderline when based on the statistical cut-off of 0.05. The effect size and direction remain approximately the same. Two reasons may, in part, account for this: (i) we did not have BNP measurements in all participants, which reduces the power to achieve a statistical threshold, (ii) a positive correlation between adiponectin and BNP is known,\(^4\) which often weakens the effect in a regression analysis.

The value of a biomarker can simplistically be seen as a clinical tool to provide diagnostic or prognostic information to help medical decision making or to provide mechanistic insights.\(^5\) As we point out, the benefit of our data should be seen in the confirmation and extension of recent evidence, that the biomarker adiponectin with a positive biological profile in experimental data, animal models, and human studies in individuals free of symptomatic cardiovascular disease.
seems to be associated with adverse outcome in manifest CAD when measured with a commercially available assay. This information, in a large epidemiological study, may help to better understand the complex pathophysiological role of adiponectin in health and disease.

References

Renate Schnabel
Johannes Gutenberg-University Mainz
Langenbeckstrasse 1
Mainz
Germany
Email: schnabelr@gmx.de

Vascular endothelial growth factor protein levels and gene expression in peripheral monocytes after stenting: a randomized comparative study of sirolimus-eluting and bare-metal stents

With great interest, we read the article by Kochiadakis et al.1 dealing with the relationship between monocyte vascular endothelial growth factor (VEGF) gene expression, VEGF serum level, and in-stent late luminal loss following stenting in stable coronary artery disease (CAD) patients. The authors demonstrate that the VEGF serum level 1 month after stenting was significantly lower in patients who received a sirolimus-eluting stent (SES) compared with those who received a bare-metal stent (BMS). Furthermore, monocyte VEGF gene expression 1 month after stenting positively correlated with in-stent late luminal loss after 6 months. This is an important study as it (i) highlights clearly detectable systemic effects of SES and (ii) underscores the usefulness of circulating monocytes as diagnostic tools.2

Kochiadakis et al. suggest that the lower VEGF level in the SES group can be attributed to the decreased VEGF gene expression of their circulating monocytes probably resulting in reduced VEGF protein production. Monocytes are certainly attractive indicators for drug-influenced gene regulation because of their easy accessibility. However, although serving as bioreactors and reservoirs for (paracrine) cytokines and chemokines during tissue repair and remodelling, monocytes/macrophages may not be regarded as important contributors to the VEGF concentration in human blood. Indeed, thrombocytes were shown to be the major source of VEGF in serum samples following its release during the in vitro clotting process.3 Elevated VEGF levels indicate local inflammation and are closely related to the presence of atherosclerotic risk factors.3 In contrast, the reduced VEGF serum level as well as the reduced VEGF monocyte level following SES implantation may rather reflect a systemic effect of rapamycin on cellular VEGF production.

Sirolimus-eluting stent-related reduction in VEGF serum levels may not only be beneficial, as proposed by Kochiadakis et al.1 Previously, it was shown that VEGF inhibition is associated with enhanced endothelial dysfunction and apoptosis.4 Likewise, the use of the VEGF inhibitor bevacizumab (Avastin®) is potentially associated with increased cardiovascular complications.5 Therefore, decreased VEGF levels following SES implantation may reflect a reduced stimulus for endothelial regeneration and may therefore be causally linked with the elevated risk for SES-related late stent thrombosis.6

A recent study highlighted the positive correlation between maximal circulating monocyte count after coronary stenting with in-stent neointimal volume after 6 month follow-up.7 Although this publication is cited by Kochiadakis et al. as an argument that monocytes contribute to neointima formation, the authors did not provide monocyte count data themselves. It would be interesting to see whether the absolute monocyte count did differ in the two study groups following stent implantation. Instead, the authors suggest that the higher monocyte VEGF gene expression in the BMS group reflects monocyte activation after stent implantation, leading to inflammatory reactions which trigger pathophysiological mechanisms and ultimately restenosis. Further investigation of functional aspects of monocytes such as adhesion or chemotaxis may be a clue to get a clearer picture of the link between monocyte activation and potential consequences for neointima formation following coronary stenting.

References

Frauke S. Czepuch
Department of Cardiology
Cardiovacular Research Institute Maastricht (CARIM)
University of Maastricht
P. Debyelaan 25, PO Box 5800
6202 AZ Maastricht
The Netherlands